## REMARKS

**A Request for a Two (2) Month Extension of Time pursuant to 37 CFR 1.136(a) and (b) is attached hereto.**

The above-captioned patent application has been carefully reviewed in light of the final Office Action to which this Amendment is responsive. Claims 1, 31 and 34 have been amended in an effort to more clearly define and particularly point out that which is regarded as the present invention. Claim 23 has been canceled and rewritten as new Claim 35 in an effort to better clarify the blood component analytical method of the above-captioned application. Claims 24-27 and 31-33 have also been amended to conform to the cancellation of Claim 23 in favor of new Claim 35. Claims 31 and 34 have been further amended to respond to Section 112 rejections made by the Examiner. To that end, it is believed that no new matter has been added to the above-captioned application.

Claims 1-11, 23-27 and 31-34 are currently pending. Each of the pending claims have been rejected in light of certain prior art. More particularly, Claims 1-4, 7-9, 11, 23-25, 31 and 33-34 have been rejected under 35 USC §102(b) as being unpatentable over Chandler (U.S. Patent No. 5,607,863) Claims 5, 6 and 26 and 27 have been rejected under 35 USC §103(a) based on the combination of Chandler, Fruitstone et al. (U.S. Patent No. 4,259,207) and Killeen et al. (U.S. Patent No. 5,166,051) and Claims 10 and 32 have rejected, also under 35 USC §103(a) based on the combination of Chandler and Killeen et al. Claims 1-11, 23-27 and 31-34 have also been rejected under 35 USC §112, 2nd paragraph. Applicant respectfully requests reconsideration on the amended claims and the following discussion.

Turning to the prior art rejections and in order to successfully anticipate under the Patent Statute, each and every claimed limitation must be found in the single cited reference. Those limitations that are not found in the reference must be notoriously well known in the field of the invention to one of sufficient (e.g., ordinary) skill.

Applicant disagrees that Chandler discloses each and every claimed limitation according to Claim 1 and therefore traverses the anticipation rejection. More particularly, Chandler fails to disclose a cell shrinkage reagent, as presently required in each of the independent claims of the above-captioned application. As described in Chandler, sodium nitrite is used to carry out hemolysis (i.e., destruction) of a cell. On the other hand, the cell shrinkage reagent that is used in the biosensor of the present invention actually shrinks a cell, wherein the shrunken cell is not destroyed. More generally, each of "hemolysis" and "shrinkage" relate to are phenomena caused by the utilization of osmotic pressure of solution. However, there are essential distinctions therebetween. First, "hemolysis" of a cell is a phenomenon occurring when a cell is dipped into a hypertonic solution. Water within the cell enters the cell wherein the cell expands and is destroyed. On the other hand, "shrinkage" of a cell is a phenomenon occurring in which the cell dipped into a hypertonic solution causes water within the cell to be shifted therefrom and the cell is contracted (i.e., shrunk). The cell itself, however, is preserved.

It appears that the Examiner believes that Chandler discloses the steps of shrinking cell components in a blood or other liquid specimen through means of sodium nitrite being held in a reagent holding part and then developing the shrunk cell components toward the chromatographic downstream direction in a mixed state along with the remainder of liquid portion of the specimen. However, Chandler fails to teach or disclose that cell components of the specimen are shrunk by means of sodium nitrite and further fails to disclose that the blood specimen is developed in a state in which the shrunk cell components are mixed. These differences are herein explained in greater detail.

First, Chandler teaches an assay device in which sodium nitride to lyse cells and extract analytes therein is present in a dried form.

A general explanation of the interaction of sodium nitride and a cell is now provided. First, sodium nitride is known as a strong oxidizing agent that reacts intensely with water at room temperature and generates sodium hydroxide. This reaction is characterized as follows: $NaNo_2+H_2O \rightarrow NaOH+NHO_2$, wherein the generated sodium hydroxide is made alkaline with sodium nitride solution.

When an alkaline solution comprising a strong base, such as sodium hydroxide, is added to protein, it is fairly well established that the alkaline solution cuts amide binding of protein wherein the protein is parted and deliquesces. Regardless of a concentration region of sodium hydroxide solution, the phenomenon that the hand to which sodium hydroxide is attached is slimy occurs due to that protein forming skin of the hand being dissolved by this reaction. It is further well-known that it is impossible to repair protein that is chemically damaged by an alkaline solution.

Accordingly, the sodium nitride of Chandler has an effect of lysing the cell membrane or the cell by a chemical reaction, and cell shrinkage, which is a primary feature of the presently claimed invention, never occurs. See col. 21, line 67 to col. 22, line 7 of Chandler.

Figure A, attached hereto, further illustrates the differences between "lysing" and "shrinkage". As shown in figure A, lysing creates a cutting of the amide binding of protein, forming a cell membrane by a chemical reaction, using sodium nitride. Cell fragments that are formed (lysed) can not be repaired by any processing, wherein the resulting cells are in a state in which their original characteristics are lost.

Contrarily and as shown in the attached figure B, "shrinkage" as defined by the present invention, indicates a state in which the cells are compressed by the function of osmotic pressure upon a cell in a state wherein substances that can penetrate the cell membrane are present in a high concentration, utilizing the nature of membrane equilibrium. As shown in figure B, the size of the shrunk cell components is smaller than the size of the original cell. However, shrunk cells are <u>not</u> crushed as in figure A

(lysing) and the resulting shrunk cell is in a state in which interstitial fluid has oozed out under the influence of osmotic pressure. This smaller sized cell retains the properties of the original cell and can also return to its original size. Therefore, "lysing" and "shrinkage" produce two entirely different sets of properties and are functionally different.

The present invention provides a biosensor in which the cell components are shrunk such that the cell components can be made smaller by a cell shrinkage agent without substantially destroying the components by the function of osmotic pressure. The shrunk cell components, as well as the remaining liquid portion of the specimen, are mixed such that clogging does not result and therefore the shrunk cell components in the liquid specimen are developed on the reaction layer in the downstream direction, chromatographically, without performing isolation. The cited reference to Chandler, which relates only lysing (destruction of the cell components) clearly fails to teach or suggest these features. Therefore, it is believed that Chandler cannot anticipate either of the independent claims of the above-captioned application. Each of Claims 1 and new Claim 35 now clearly recite these features. Claims 2-4, 7-9, 11, 24, 25, 31, 33 and 34 are believed to be allowable for the same reasons. Reconsideration is respectfully requested.

Turning now to the Section 103 rejections and in order to successfully maintain a "*prima facie*" obviousness rejection under the Statute, each and every claimed limitation must be found in or be suggested, either singly or in combination, by the cited prior art. Those features that are not found or are suggested by the prior art must be notoriously well known in the field of the invention at the time thereof. In addition, it is axiomatic that a motivation be fond in the prior art as a whole to one of sufficient skill in the field of the invention to make the purported combination. The motivation cannot be the result of impermissible hindsight; that is, advance knowledge of the invention wherein

piecemeal substitution of features is made without regard to the entirety of the teachings of the cited art. Put another way, the purported combination cannot destroy or drastically change the teachings of the references, particularly when at least one reference teaches away from such a combination.

Claims 1 and 23 (now Claim 35) have previously been discussed with regard to Chandler. As discussed herein, Chandler fails to describe or suggest employing a cell shrinkage reagent that shrinks cell components of a liquid specimen wherein the properties of the cell are not destroyed, but the components are made smaller. The cell components as well as the liquid specimen are mixed and permeated chromatographically downstream toward a reaction layer. Each of the foregoing claims have been amended to more clearly articulate the shrinking function wherein Chandler also fails to disclose or suggest that the shrunk cell components, as well as the remainder of the liquid specimen, are mixed and permeated chromatographically downstream to the reaction layer of the biosensor.

Neither of the secondary references to Killeen et al. or Fruitstone et al. discloses nor teaches those missing features. Therefore, their combination fails to produce the claimed invention and an obviousness rejection cannot be maintained under the Statute. In addition and as previously noted, the Killeen sensor actually prevents cell components from moving with the liquid specimen in that minute pores on a membrane perform a screening or filtering function. That is, the object of Killeen et al., is to prevent cell components of the specimen from reaching the reaction layer, a result contrary from that of the present invention. Since Claims 1 and 35 are believed to be allowable, Claims 5, 6, 10, 26, 27 and 32 are also believed to be patentably distinct for the same reasons. Reconsideration is therefore respectfully requested.

Each of the independent Claims 1 and 23 (now rewritten as new Claim 35), have been amended to further clarify and distinguish the present invention. Support is found in the present disclosure and it is believed that no new matter has been added.

Turning to the Section 112 rejections, Applicant has now further amended each of the independent claims in an effort to clarify and distinctly point out the invention. With regard to Claim 1, Applicant now specifies that the carrier of the biosensor carries the cell shrinkage reagent and also further specifies that the liquid specimen includes the cell components that are shrunk by the reagent. Applicant further amends this claim to set forth that the shrunk cell components together with the liquid specimen are permeated into the reaction layer of the biosensor wherein analysis occurs.

Claim 23 has been canceled and now has been rewritten as new Claim 35. This claim now recites the structural features of the biosensor for use in the analytical method in the preamble and delineates the method steps more completely in the amended claim in which the steps of shrinking the cell components of the blood specimen by dissolving of a cell shrinkage agent disposed on at least a portion of an area that is defined by a specimen addition part and a reagent holding part. Moreover, the method further includes the additional steps of chromatographically permeating the shrunk cell components with the blood specimen in a mixed state, marking the analyte in the permeated blood specimen with reagent that has been held in the reagent holding part of the biosensor and carrying out a reaction at the reaction layer of the biosensor wherein the reaction takes place between the mixed solution and cell components and the eluted reagent that has been dissolved from the reagent holding part.

Each of the antecedent bases problems noted by the Examiner in items 5-9 of the pending Office Action. Moreover, the issues in item 10 of the outstanding Office Action are believed to be cured by way of the present amendment to new Claim 35 through a more precise delineation of the method steps and through defining the structure of the biosensor and the blood specimen. As noted previously, a single specimen that includes liquid and cell components is herein recited. Finally, Claims 31 and 35 have been amended to specify that the concentration of the cell shrinkage reagent is "in the range of about 0.1 to about 5.0M".

It is believed ample support is provided in the present application for each of the above-noted amendments and that no new matter has been added. See, for example, page 22, line 9 – page 23, line 6 as well as page 23, lines 7-19. It is now believed that each of the claims is now in an allowable condition and reconsideration is respectfully requested.

In summary, it is believed the above-captioned patent application is in an allowable condition. Entry of this amendment and an expedited Notice of Allowability are respectfully requested.

If the Examiner wishes to expedite disposition of the above-captioned patent application, he is invited to contact Applicant's representative at the telephone number below. In view of the above amendment, applicant believes the pending application is in condition for allowance.

Applicant believes a fee is due with this response for purposes of the request for a two (2) month extension. However, if additional fees are due, please charge our Deposit Account No. 50-0289, under Order No. 967_026RCE from which the undersigned is authorized to draw.

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Respectfully submitted,

By _____

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Fig.A

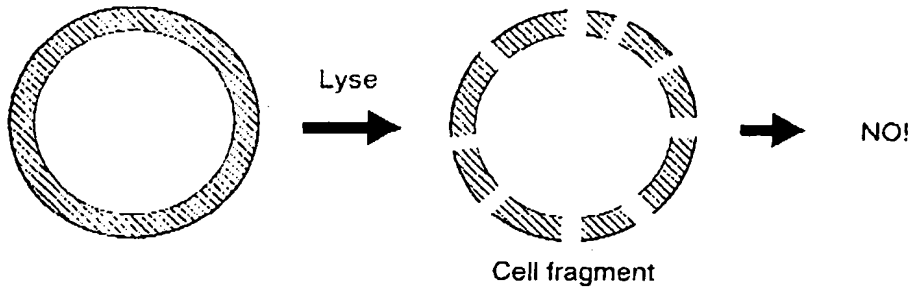


Fig.B